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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,608	CASSART ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 10-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/24/03;08/30/06*.
4) ☐ nterview Summary (PTO-413) Paper No(s)/Mail Date.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant elected with traverse of group E, claims 6-9, but did not elect a specific sequence as required, in the response of 08/29/06.

The traverse is on the ground that SEQ ID NO:10 and 35 should be rejoined with SEQ ID NO:2, because they are fusion proteins comprising SEQ ID NO:2 and an expression fusion partner (SEQ ID NO:10) or with a peptide tag (SEQ ID NO:35).

After review and reconsideration, SEQ ID NO:10 is withdrawn from groups C and D, and rejoined with SEQ ID NO:2 in groups A and B. Thus groups A and B, claims 1-5, 14-16 are drawn to a method for treating and preventing, respectively, colorectal, breast or lung cancer, using the polypeptide SEQ ID NO:2, or a fusion protein thereof, SEQ ID NO:10, or SEQ ID NO:35 as cited in the specification.

In a telephonic interview with ERIC KRON on 09/19/06, Applicant elected SEQ ID NO:25. Further, on 09/26/06, at the request of the Examiner, Applicant kindly submitted a communication identifying the peptides used in Example 10, in relation to SEQ ID NO:25. As indicated in the communication, SEQ ID NO:25, a nine amino acid peptide, is a predicted HLA binding epitope, having as start position amino acid 99 of SEQ ID NO:2 (the instant specification, pages 66-68), and is a fragment of peptide 25 used in Example 10 (the instant application, page 71, first paragraph), which is amino acids 97-111 of SEQ ID NO:2, as shown in the table on page 72 or the parent Applicant serial No: 10/226872.

Accordingly, group E, claims 6-9, SEQ ID NO: 25 are examined in the instant application.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9 are rejected as being indefinite for the use of designation "CASB7439" as the sole means of identifying the claimed antigen. The use of laboratory designation only to identify a particular antigen renders the claim indefinite because different laboratories may use the same laboratory designations to define completely distinct antigens. Amendment of the claims to include physical and/or functional characteristics of "CASB7439" which unambiguously define "CASB7439", for example, a sequence identification number, is required.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that the present invention relates to CASB7349 polypeptides comprising an amino acid sequence which has at least 70%, 80%, 90%, 95% or 97-99% identity to that of SEQ ID NO:2 (p.6, lines 14-17).

In view of the teaching in the specification, CASB7349 without being accompanied by a sequence identification number encompasses a genus of variants of SEQ ID NO:2, with unknown structure and function, provided they have at least 70%, 80%, 90%, 95% or 97-99% identity to that of SEQ ID NO:2. Thus the claims 6-9 encompass a method for inducing an immune response to a **genus of variants** of SEQ ID NO:2, using a peptide fragment of SEQ ID NO:2.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated,

> does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In this case, the specification does not describe CASB7439 protein in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide sufficient structure or common structure, other than SEQ ID NO:2, to support the broad breath of the claimed genus. Nor is there any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polypeptide, SEQ ID NO:2, this does not provide a description of CASB7439 protein, that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe CASB7439 protein, by the standards shown in the example in Lilly. The specification describes only a single polypeptide SEQ ID NO:2. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The specification does not provide an adequate written description of CASB7439 protein that is required to practice the claimed invention. Thus, the specification does not meet the 112, first paragraph written description requirement, and one of skill in the art would reasonably conclude that Applicant did not have possession of the claimed CASB7439 protein at the time the invention was made. Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 6-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that a method for inducing an immune response to CASB7439 encompasses a method for **treating cancer.** Further a method for inducing an immune response, using a peptide fragment of SEQ ID NO:2, as claimed in claims 6, 8, 9 encompasses a method for treating cancer, using **any** peptide fragment of SEQ ID NO:2.

The following *Wands* factors have been considered when the 112, first paragraph, enablement rejection was made:

The breadth of the claims

The breadth of the claims is broad. The claims encompass a method for treating cancer via induction of an immune response to SEQ ID NO:2 or variants thereof, using any fragment of SEQ ID NO:2 or the peptide SEQ ID NO:25.

The nature of the invention

The nature of the invention is complex, comprising cancer treatment using peptides for activating specific cytotoxic T cells, or for producing antibodies that could kill cancer cells in cancer patients.

The level of one of skill in the art

Although the level of skill in the field of molecular pathology is high, it would be undue experimentation for one of skill in the art to practice the claimed invention.

The level of predictability of the art

The level of unpredictability in the art is high.

One cannot predict that SEQ ID NO:25 or any fragments of SEQ ID NO:2 could be used for producing CTLs or antibodies specific for SEQ ID NO:2, effective for cancer treatment, because 1) Cancer treatment is unpredictable, and 2) One cannot predict that SEQ ID NO:2 is adequately immunogenic and exposed in sufficient quantities on the surface of malignant cells in vivo, such that CTLs could recognize and lyse said malignant cells.

It is well known in the art that cancer treatment is highly unpredictable. It is also well known that the problem with tumor tolerance and downregulation of the antigen or the loss of surface Class I MHC is common. For example, Smith RT, 1994 (Clin Immunol, 41(4): 841-849), teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). White et al, 2001, Ann Rev Med, 52: 125-145, teach that antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Boon, 1992 (Adv Can Res, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at

least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Further, Kirkin et al, 1998 (APMIS, 106 : 665-679) teach that although several peptides of melanoma associated antigens have been identified as recognized by CTLs in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (see Kirkin et al, 1998, especially p.666, second column, second paragraph, last 6 lines). Similarly, Gaiger, A et al, 2000 (Blood, 96(4): 1480-1489) teach that although MHC binding peptides of WT1 protein induce WT1 peptide specific cytotoxic T cells, that specifically lyse cancer cell lines overexpressing WT1, and also produce WT-1 specific antibodies in patients with acute myeloid leukemia, immunization with the WT1 peptides did not show any effect on WT1 cancer growth in vivo. Thus, in view of the teaching in the art, one cannot predict that SEQ ID NO: 25 could elicit specific CTLs with high affinity, or antibodies that recognize and kill in vivo malignant cells.

Further, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell, 1995 (J. NIH Res, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to

prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler, 1995 (Cancer Biotherapy, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

In addition, one cannot predict that any fragments of SEQ ID NO:2 could produce antibody that recognizes SEQ ID NO:2 on cancer cell surface, or could bind to MHC molecule and elicit sufficient T cells response, such that they could be used in the claimed method. Roitt et al, 1998, (Immunology, 4th ed, Mosby, London, p. 7.7-7.8) teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. Roitt et al teach that it is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. Roitt et al teach that these regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). Roitt I et al further teach that only a minority of peptide fragments from a protein antigen are able to bind to a particular MHC molecule (p.7.9).

Moreover, even if SEQ ID NO:2 were expressed in sufficient quantity on colon cancer cells to be recognized and lysed by CTLs, one cannot predict that the expression of CASB7439 variants of SEQ ID NO:2 would be the same as that of SEQ ID NO:2, i.e. whether CASB7439 variants of SEQ ID NO:2 would be overexpressed on colon cancer cells, to be recognized and

lysed by CTLs, because it is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type. For example, Schmid S et al, 2001 (J comparative Neurology, 430(2): 160-71), teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996 (Mol Brain Res, 42: 1-17), teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2). Thus in view of the teaching in the art one cannot predict that the variants of SEQ ID NO:2 would express or overexpress in cancer tissue as compared to normal control tissue, to be recognized and lysed by CTLs.

Working example and The amount of direction provided by the inventor

The specification discloses that the CASB7439 protein is overexpressed in primary colon cancer as compared to normal mucosa control (Example 11 on page 71). The specification discloses that SEQ ID NO:25 is one of the predicted epitopes that bind to HLA molecules (p.66-67).The specification discloses that peptide 16, 23, 24, 25 which are fragments of CASB7439 protein SEQ ID NO:2 activate T cells from 3 healthy donors, which T cells recognize full length SEQ ID NO:2 (Example 10, on pages 68-71). The specification discloses that two CASB7439 peptides, peptide 1-2 induces antibody specific for the CASB7439 peptide (p.72). The

specification contemplates testing the effect of the stimulated T cells on tumor cells transfected with cDNA encoding SEQ ID NO:2 (p.64, last two paragraphs, bridging p.65).

The specification however does not have any objective evidence of successful treatment of cancer by CTLs or antibodies induced by administration of the peptide SEQ ID NO: 25, or of any peptide fragment of SEQ ID NO:2. The specification does not have objective evidence that sufficient and high affinity CTLs or antibodies are produced in cancer patients with cancer burden, where the problem of cancer tolerance, with suppression of CTLs and/or antibody production, is common.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

Conclusions

No claims are allowed.

The closiest prior art is Johnson et al, GenBank Accession No: S11562, Nature, 1990, 346: 858-861, which teach a 260 amino acid polypeptide, which polypeptide contains the nine amino acid peptide SEQ ID NO:25 of the claimed invention (MPSRCH 2006 search report, us-10-650-608-25.rpr, pages 1-3). Jonhson et al, however, do not teach or suggest the specific peptide fragment SEQ ID NO:25, nor a method for inducing an immune response to CASB7439, or treating cancer patients, using a peptide fragment of SEQ ID NO:2 or SEQ ID NO:25.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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MINH TAM DAVIS
September 20, 2006

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER